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[54]发明名称 R－沙丁胺醇酒石酸盐的制备方法

[57]摘要

本发明是R－沙丁胺醇酒石酸盐的制备方法，它是以消旋体沙丁胺醇为原料，按摩尔比为1：4～1：1的比例把光学纯拆分剂L－(＋)－酒石酸和消旋体沙丁胺醇混合溶解或分别溶解在水、醇或酮中，搅拌下加热回流10～30分钟或加热回流至澄清，降温至室温，析出非对映异构体固体盐，过滤，得到R－沙丁胺醇酒石酸盐，产品纯度高，结晶性能和稳定性良好，e.e.大于99%，收率大于50%。本发明还有原料易得，工艺简单等特点。

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1. R-沙丁胺醇酒石酸盐的制备方法，其特征在于以消旋体沙丁胺醇为原料，按拆分剂和消旋体沙丁胺醇摩尔比为 1：4~1：1 的比例把光学纯拆分剂 L-（+）-酒石酸和消旋体沙丁胺醇混合溶解或分别溶解在水、醇和酮中的一种或它们的混合溶剂中，溶剂的用量为 15～85ml/g 溶质，搅拌下加热回流 10~30 分钟或加热回流至澄清，降温至室温，析出非对映异构体固体盐，过滤出固体盐，得到 R-沙丁胺醇酒石酸盐。

2. 根据权利要求 1 所述的 R-沙丁胺醇酒石酸盐的制备方法，其特征在于用天然的 L-（+）-酒石酸作为拆分剂直接拆分消旋体沙丁胺醇制备 R-沙丁胺醇酒石酸盐。

3. 根据权利要求 1 所述的 R-沙丁胺醇酒石酸盐的制备方法，其特征在于过滤得到的固体盐，再用水、醇和酮的混合溶剂重结晶 1~6 次，得到 R-沙丁胺醇酒石酸盐。

4. 根据权利要求 3 所述的 R-沙丁胺醇酒石酸盐的制备方法，其特征在于混合溶剂的体积比例为水：醇或水：酮＝1：10～35。

5. 根据权利要求 1 或 2 或 3 或 4 所述的 R-沙丁胺醇酒石酸盐的制备方法，其特征在于所用的醇为脂肪醇，所用的酮为脂肪酮。

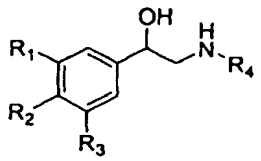
6. 根据权利要求 5 所述的 R-沙丁胺醇酒石酸盐的制备方法，其特征在于所用的醇为甲醇、乙醇、丙醇、丁醇，酮为丙酮、丁酮、环己酮。

7. 根据权利要求 1 或 2 或 3 或 4 或 5 或 6 所述的 R-沙丁胺醇酒石酸盐的制备方法所制取的产品主要用于哮喘病。

# R-沙丁胺醇酒石酸盐的制备方法

本发明属于光学纯化合物的制备领域，尤其是涉及 R-沙丁胺醇酒石酸盐的制备方法。

肾上腺素类β-激动剂都具有一个手性中心和两个对映异构体，它们是一类非常有用的气管炎抑制剂。肾上腺素类β-激动剂的分子结构式如下：




a. $R_1$=H, $R_2$=OH, $R_3$=$CH_2OH$, $R_4$=t-Bu
b. $R_1$=H, $R_2$=OH, $R_3$=$CH_2OH$, $R_4$=$(CH_2)_6$-O-$(CH_2)_4$-$C_6H_5$
c. $R_1$=H, $R_2$=$R_3$=OH, $R_4$=$CH_3$
d. $R_1$=H, $R_2$=$R_3$=OH, $R_4$=$CH(CH_3)_2$
e. $R_1$=H, $R_2$=$R_3$=p-$CH_3C_6H_4CO_2$, $R_4$=t-Bu
f. $R_1$=H, $R_2$=$NH_2$, $R_3$=OH, $R_4$=t-Bu
g. $R_1$=$R_3$=OH, $R_2$=H, $R_4$=$CH(CH_3)_2$
h. $R_1$=$R_3$=OH, R=H, $R_4$=t-Bu
i. $R_1$=$R_3$=$(CH_3)_2NCO_2$, $R_2$=H, $R_4$=t-Bu
j. $R_1$=$R_3$=Cl, $R_2$=$NH_2$, $R_4$=t-Bu

其中的沙丁胺醇即化合物α-[[（1，1-二甲基乙基-）氨基]甲基]-4-羟基-1，3-苯二甲醇（上面 a），是一种非常有效的肾上腺素类β-激动剂，它对β-1 和β-2 受体具有很高的选择性，目前广泛用于哮喘的治疗。此类β-激动剂较其他β受体激动剂有毒副作用小的特点。药物学研究表明，R-沙丁胺醇即α-[[（1，1-二甲基乙基-）氨基]甲基]-4-羟基-1，3-苯二甲醇的（-）-对映体，较其（+）-对映体，即 S-沙丁胺醇的药效高出 80 倍（Hartley and Middlemis, *J. Med.Chem.* **14**, *895~896*, **1997**），而且其（-）-对映体在体内的吸收率也要比其（+）-对映体高(Wetterlin, *J. Med.Chem.* **15**, *1182~1183*, **1972**)。

目前，外消旋体沙丁胺醇的合成工艺比较成熟。光学纯沙丁胺醇还主要是用化学拆分方法制备。一种是直接拆分法，即直接拆分消旋体沙丁胺醇，以萘普生为拆分剂，收率 15%，e.e.（对映体过量值）85%（*Sepc. Chem.* **15**, *249~253*, **1995**）。另外一种就是间接拆分法，即拆分沙丁胺醇前体（*J. Med. Chem.* **14**, *895~896*, **1971**、US5545745、US5399765 和 WO95/32178），然后再通过几步化学反应得到最终的光学纯沙丁胺醇。

本发明的目的在于提供一种 R-沙丁胺醇酒石酸盐的制备方法，以得到高纯度、结晶性能和稳定性良好的光学纯 R-沙丁胺醇的 L-（+）-酒石酸盐，且原料易得，工艺简便。

本发明的目的是通过如下技术方案来实现的：

以消旋体沙丁胺醇为原料，按拆分剂和消旋体沙丁胺醇摩尔比为 1：4~1：1 的比例把光学纯拆分剂 L-（+）-酒石酸和消旋体沙丁胺醇混合溶解或分别溶解在水、醇和酮中的一种或它们的混合溶剂中，溶剂的用量为 15～85ml/g 溶质，搅拌下加热回流 10~30 分钟或加热回流至澄清，降温至室温，析出非对映异构体固体盐，过滤出固体盐，得到 R-沙丁胺醇酒石酸盐。

上述方案中，过滤得到的固体盐，再用水、醇和酮的混合溶剂重结晶 1~6 次，得到 R-沙丁胺醇酒石酸盐。

上述方案中，混合溶剂的体积比例为水：醇或水：酮＝1：10～35。

上述方案中，所用的醇为甲醇、乙醇、丙醇、丁醇等脂肪醇，酮为丙酮、丁酮、环己酮等脂肪酮。

目前有很多的药物以酒石酸盐的形式上市。本发明以天然 L-（+）-酒石酸为拆分剂，直接拆分消旋体沙丁胺醇，经过多次重结晶得到高纯度、结晶性能和稳定性良好的光学纯 R-沙丁胺醇的 L-（+）-酒石酸盐，其中所含的沙丁胺醇的 e.e.大于 99%，收率大于 50%（基于消旋体一半计算）。H-NMR 表明此盐中 R-沙丁胺醇和 L-（+）-酒石酸的摩尔比例是 2：1。本发明还有原料易得，工艺简便等特点。

R-沙丁胺醇的 L-（+）-酒石酸盐在 X 射线粉末衍射图谱中具有如下主峰。

| $d_{hkl}$ 值/Å | 相对强度 |
|---|---|
| 16.05 | w |
| 8.11 | vs |
| 7.89 | s |
| 7.25 | m |
| 6.46 | m |
| 5.30 | m |
| 5.01 | m |
| 4.87 | m |
| 4.44 | s |
| 3.93 | vs |
| 3.80 | m |
| 3.62 | m |
| 3.42 | m |
| 3.24 | m |
| 3.10 | w |
| 2.86 | w |
| 2.71 | w |
| 2.49 | w |
| 2.32 | w |
| 2.13 | w |

下面是本发明的实施例，本发明不仅限于所述实施例。

实施例中，固体收率按 L-（+）-酒石酸和沙丁胺醇的摩尔比例 1：2 为基准

计算，两种构型的沙丁胺醇的收率以消旋体的一半为基准计算。

实施例中，对映体过量值（e.e.）通过 HPLC 测定的，具体参数如下：

手性色谱柱：OA-4900，5μ，4.6×250mm

流 动 相：正己烷：二氯甲烷：甲醇：三氟醋酸（240：140：20：1）

检测波长：280nm

实施例一

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 2ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 3ml 乙醇中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.141g 白色非对映异构体固体盐，收率 95%，其中所含的 R-沙丁胺醇的光学纯度为 58.4%e.e.。

实施例二

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 3ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 3ml 乙醇中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.117g 白色非对映异构体固体盐，收率 89%，其中所含的 R-沙丁胺醇的光学纯度为 57.1%e.e.。

实施例三

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 4ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 3ml 丙酮中，然后将两者混合，加热回流 30 分钟，降至室温，过滤得到 0.139g 白色非对映异构体固体盐，收率 106%，其中所含的 R-沙丁胺醇的光学纯度为 41.3%e.e.。

实施例四

将 0.126g(0.84mmol) L-（+）-酒石酸溶解在 3ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 3ml 乙醇中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.056g 白色非对映异构体固体盐，收率 43%，其中所含的 R-沙丁胺醇的光学纯度为 69.5%e.e.。

实施例五

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 1ml 水中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 10ml 丙酮中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.067g 白色非对映异构体固体盐，收率 51%，其中所含的 R-沙丁胺醇的光学纯度为 71.0%e.e.。

实施例六

将 0.063g(0.42mmol) L-（+）-酒石酸和 0.2g(0.84mmol)消旋体沙丁胺醇溶解在 10ml 乙醇（95%）中，加热回流至澄清，然后降至室温，过滤得到 0.125g 白色非对映异构体固体盐，收率 95%，其中所含的 R-沙丁胺醇的光学纯度为 58.4%e.e.。

实施例七

将 0.063g(0.42mmol) L-（+）-酒石酸和 0.2g(0.84mmol)消旋体沙丁胺醇溶解

在 10ml 乙醇中，加热回流至澄清，然后降至室温，过滤得到 0.224g 白色非对映异构体固体盐，收率 171%，其中所含的 R-沙丁胺醇的光学纯度为 10.6%e.e。

实施例八

将 0.063g(0.42mmol) L-（+）-酒石酸和 0.2g(0.84mmol)消旋体沙丁胺醇溶解在 5ml 乙醇（95%）中，加热回流至澄清，然后降至室温，过滤得到 0.135g 白色非对映异构体固体盐，收率 103%，其中所含的 R-沙丁胺醇的光学纯度为 55.1%e.e.。

实施例九

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 4ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 3ml 丁酮中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.105g 白色非对映异构体固体盐，收率 80%，其中所含的 R-沙丁胺醇的光学纯度为 60.5%e.e.

实施例十

将 0.035（0.23mmol）L-(+)-酒石酸溶解在 3ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 4ml 乙醇中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.079g 白色非对映异构体固体盐，收率 77%，其中所含的 R-沙丁胺醇的光学纯度为 63.6%e.e.。

实施例十一

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 3ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 4ml 环己酮中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.071g 白色非对映异构体固体盐，收率 54%，其中所含的 R-沙丁胺醇的光学纯度为 77.3%e.e.。

实施例十二

将 0.063g(0.42mmol) L-（+）-酒石酸溶解在 3ml 甲醇中，0.2g(0.84mmol)消旋体沙丁胺醇溶解在 3ml 正丁醇中，然后将两者混合，加热回流 10 分钟，降至室温，过滤得到 0.111g 白色非对映异构体固体盐，收率 84%，其中所含的 R-沙丁胺醇的光学纯度为 63.2%e.e.。

实施例十三

将 0.32g(2.13mmol) L-（+）-酒石酸和 1.00g(4.18mmol)消旋体沙丁胺醇溶解在 25ml 乙醇（95%）中，加热回流至澄清，然后降至室温，过滤得到 0.683g 白色非对映异构体固体盐，收率 104%，其中所含的 R-沙丁胺醇的光学纯度为 56.5%e.e.。取 0.660g 上步得到的 56.5%e.e 的非对映异构体固体盐，用 1ml 水和 21ml 乙醇重结晶，得到 0.414g 白色非对映异构体固体盐，重结晶收率为 63%，其中所含的 R-沙丁胺醇的光学纯度为 85.8%e.e.。取 0.398g 经一次重结品 85.8%e.e 的非对映异构体固体盐，用 0.6ml 水和 17ml 乙醇重结晶，得到 0.348g 白色非对映异构体固体盐，重结晶收率为 88%，其中所含的 R-沙丁胺醇的光学纯度为 94.2%e.e.。取 0.332g 经一次重结晶 94.2%e.e 的非对映异构体固体盐，用 0.5ml 水和 10ml 乙醇重结晶，得到 0.332g 白色非对映异构体固体盐，重结晶收率为

85%，其中所含的 R-沙丁胺醇的光学纯度为 96.7%e.e.。

实施例十四

将 1.30g(2.13mmol) L-（+）-酒石酸和 4.00g(4.18mmol)消旋体沙丁胺醇溶解在 100ml 乙醇（95%）中，加热回流至澄清，然后降至室温，过滤得到 3.738g 白色非对映异构体固体盐，收率 141%，其中所含的 R-沙丁胺醇的光学纯度为 19.5%e.e.。将得到的非对映异构体固体盐重结晶四次，得到 97.6%e.e.的非对映异构体固体盐，重结晶的收率是 38%。a）取 97.6%e.e 非对映异构体固体盐，用 3ml 甲醇，0.2ml 水，4ml 乙醇重结晶，得到 0.185g 白色非对映异构体固体盐，重结晶收率为 84%，其中所含的 R-沙丁胺醇的光学纯度为 99.2%e.e.。b）取 97.6%e.e 非对映异构体固体盐，用 0.5ml 水，0.3ml 甲醇，5ml 丙酮重结晶，得到 0.185g 白色非对映异构体固体盐，重结晶收率为 84%，其中所含的 R-沙丁胺醇的光学纯度为 99.3%e.e.，$[\alpha]_D^{20}$=-24.3°（c=0.25，水），X 射线粉末衍射图谱中具有如下主峰：

| $d_{-1}$ 值/Å | 相对强度 |
|---|---|
| 16.05 | w |
| 8.11 | vs |
| 7.89 | s |
| 7.25 | m |
| 6.46 | m |
| 5.30 | m |
| 5.01 | m |
| 4.87 | m |
| 4.44 | s |
| 3.93 | vs |
| 3.80 | m |
| 3.62 | m |
| 3.42 | m |
| 3.24 | m |
| 3.10 | w |
| 2.86 | w |
| 2.71 | w |
| 2.49 | w |
| 2.32 | w |
| 2.13 | w |

Abstract

The invention relates to a process for preparing R-salbutamol tartrate wherein R-salbutamol tartrate is obtained from racemic salbutamol through dissolving together or respectively optically splitting the agent of L-(+)-tartaric acid and racemic salbutamol in molar ratio of 1:4 to 1:1 in water, alcohol, or ketone, then stirring while heating under reflux for 10-30 minutes or until it is clear, cooling to room temperature, isolating the diastereomer solid salt, and then filtering. The product has high purity and favourable crystallinity and stability, e.e more than 99%, output rate more than 50%. The invention has, inter alia, the features of simplicity to obtain the raw material and a simple process.

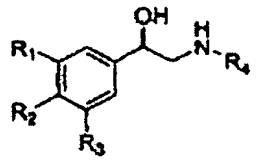
## Claims

1. Process for preparing R-salbutamol tartrate wherein R-salbutamol tartrate is obtained from racemic salbutamol through dissolving together or respectively optically splitting the agent of L-(+)-tartaric acid and racemic salbutamol in molar ratio of 1:4 to 1:1 in water, alcohol, or ketone or a mixture thereof, in which the amount of dissolvent is 15-85 ml per gram of solute, then stirring while heating under reflux for 10-30 min or until it is clear, cooling to room temperature, isolating the diastereomer solid salt, and then filtering out the solid salt.
2. Process according to Claim 1, wherein natural L-(+)-tartaric acid is used as the splitting agent to directly split racemic salbutamol to prepare R-salbutamol tartrate.
3. Process according to Claim 1, wherein R-salbutamol tartrate is obtained by recrystallizing the solid salt obtained by filtration for 1-6 times with the dissolved mixture of water, alcohol and ketone.
4. Process according to Claim 3, wherein the volume ratio of water to alcohol or water to ketone is 1:10-35.
5. Process according to any one of Claims 1 to 4, wherein the alcohol used is aliphatic alcohol and the ketone used is aliphatic ketone.
6. Process according to Claim 5, wherein the alcohol used is selected from methanol, ethanol, propanol, butanol, and the ketone used is selected from acetone, butanone, cyclohexanone.
7. Product obtained by the process for preparing R-salbutamol tartrate according to any one of Claims 1 to 6 is used for treating asthma.

# Process for preparing R-salbutamol tartrate

The invention relates to the field of preparing the optically pure compound, particularly to a process for preparing R-salbutamol tartrate.

The adrenalin β-agonists have one chiral centre and two enantiomers; they are effective inhibitors of tracheitis. The chemical formula of adrenalin β-agonist is as follows:



a. $R_1$=H, $R_2$=OH, $R_3$=$CH_2OH$, $R_4$=t-Bu

b. $R_1$=H, $R_2$=OH, $R_3$=$CH_2OH$, $R_4$=$(CH_2)_6$-O-$(CH_2)_4$-$C_6H_5$

c. $R_1$=H, $R_2$= $R_3$= OH, $R_4$=$CH_3$

d. $R_1$=H, $R_2$= $R_3$= OH, $R_4$=$CH(CH_3)_2$

e. $R_1$=H, $R_2$= $R_3$=p-$CH_3C_6H_4CO_2$, $R_4$=t-Bu

f. $R_1$=H, $R_2$=$NH_2$, $R_3$=OH, $R_4$=t-Bu

g. $R_1$=$R_3$=OH, $R_2$=H, $R_4$= $CH(CH_3)_2$

h. $R_1$=$R_3$=OH, R=H, $R_4$=t-Bu

i. $R_1$=$R_3$=$(CH_3)_2NCO_2$, $R_2$=H, $R_4$=t-Bu

j. $R_1$=$R_3$=Cl, $R_2$=$NH_2$, $R_4$=t-Bu

in which salbutamol, namely the compound α-[{(1,1-bimethylethyl-)amino}methyl]-4-hydroxy-1,3-phenyldicarbinol (a. above), is a kind of effective adrenalin β-agonist, and it has high selectivity on β1 and β2 receptors, and it is widely used for treating asthma nowadays. This kind of β-agonist has the feature of less toxicity and fewer side-effects than others. It is proved by pharmacological study that R-salbutamol is the (-)-enantiomer of α-[{(1,1-bimethylethyl-)amino}methyl]-4-hydroxy-1,3-phenyldicarbinol, and that the drug effect of R-salbutamol is 80 times higher than that of (+)-enantiomer, namely S-salbutamol (Hartley and Middlemis, *J Med. Chem.*14, 895-896, 1997), and that the absorption rate of (-)-enantiomer in vivo is better than that of (+)-enantiomer (Wetterlin, *J Med. Chem.* 15, 1182-1183, 1972).

Currently, the process for synthesizing racemic salbutamol has relatively developed. The optically pure salbutamol is made mainly by the method of chemical splitting. One method is direct splitting, namely to directly split the racemic salbutamol with Epsom as the splitting agent, with an output rate of 15% and an e.e (excessive value of enantiomer) of 85% (*Sepc. Chem* 15, 249-253, 1995). The other method is indirect splitting, namely to split the precursor of salbutamol (*J Med Chem.* 14, 895-896, 1971, US5545745, US5399765 and WO95/32178), then the final optically pure salbutamol can be obtained

by several chemical reactions.

One object of the invention is to provide a process for preparing R-salbutamol tartrate to obtain optically pure R-salbutamol having high purity and favourable crystallinity and stability, with simplicity to obtain the raw material and a simple process.

The object of the invention is achieved by technical solution as follows:

R-salbutamol tartrate is obtained from racemic salbutamol through dissolving together or respectively optically splitting the agent of L-(+)-tartaric acid and racemic salbutamol in molar ratio of 1:4 to 1:1 in water, alcohol, or ketone, or a mixture thereof, in which the amount of dissolvent is 15-85 ml per gram of solute, then stirring while heating under reflux for 10-30 min or until it is clear, cooling to room temperature, isolating the diastereomer solid salt, and then filtering out the solid salt..

In the aforenamed technical solution, R-salbutamol tartrate is obtained by recrystallizing the solid salt obtained by filtration for 1-6 times with the dissolved mixture of water and alcohol and ketone.

In the aforenamed technical solution, the volume ratio of water to alcohol or water to ketone in the dissolved mixture is 1:10-35.

In the aforenamed technical solution, the alcohol used is selected from the aliphatic alcohol of methanol, ethanol, propanol, butanol and so on, and the ketone used is selected from the aliphatic ketone of acetone, butanone, cyclohexanone and so on.

There are currently several drugs coming onto the market in the form of tartrate. Optically pure R-salbutamol L-(+)- tartrate having high purity and favourable crystallinity and stability can be obtained by directly splitting dl-salbutamol with natural L-(+)- tartrate as the splitting agent, and recrystallizing several times in the invention, in which the e.e of salbutamol contained is more than 99% and the output rate is more than 50% (calculated on the basis of half of the raceme). It is shown by H-NMR that the molar ratio of R-salbutamol to L-(+)-tartaric acid is 2:1. The invention has, inter alia, the features of simplicity to obtain the raw material and a simple process.

It is shown in X-ray power diffraction pattern that R-salbutamol tartrate has the main peak as follows:

| The value of $d_{.1}$/ angstrom | Comparative intensity |
|---|---|
| 16.05 | w |

| | |
|---|---|
| 8.11 | vs |
| 7.89 | s |
| 7.25 | m |
| 6.46 | m |
| 5.30 | m |
| 5.01 | m |
| 4.87 | m |
| 4.44 | s |
| 3.93 | vs |
| 3.80 | m |
| 3.62 | m |
| 3.42 | m |
| 3.24 | m |
| 3.10 | w |
| 2.86 | w |
| 2.71 | w |
| 2.49 | w |
| 2.32 | w |
| 2.13 | w |

The examples of the invention are as follows, but the invention is not limited to the aforenamed samples.

In the examples, the output rates of solids are calculated on the basis of 1:2 molar ratio of L-(+)- tartrate and salbutamol. The output rates of two configurations of salbutamol are calculated on the basis of half of the racema.

In the examples, the excessive value of enantiomer (e.e) is measured by HPLC. The specific parameters are as follows:

The chiral chromatographic column: OA-4900, 5μ, 4.6 x 250 mm

Moving phase: hexane: dichloromethane: methanol: trifluoroacetic acid (240:140:20:1)

The determining wavelength: 280nm

Example 1

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 2 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 3 ml ethanol, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.141 g white diastereomer solid salt was obtained by filtration with an output rate of 95%, in which the optical purity of R-salbutamol contained was 58.4% e.e.

Example 2

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 3 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 3 ml ethanol, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.117 g white diastereomer solid salt was obtained by filtration with an output rate of 89%, in which the optical purity of R-salbutamol contained was 57.1% e.e.

Example 3

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 4 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 3 ml acetone, both of them were mixed, the mixture was heated under reflux for 30 minutes, the mixture was cooled to room temperature, and then 0.139 g white diastereomer solid salt was obtained by filtration with an output rate of 106%, in which the optical purity of R-salbutamol contained was 41.3% e.e.

Example 4

0.126 g (0.84mmol) L-(+)- tartrate was dissolved in 3 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 3 ml ethanol, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.056 g white diastereomer solid salt was obtained by filtration with an output rate of 43%, in which the optical purity of R-salbutamol contained was 69.5% e.e.

Example 5

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 1 ml water and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 10 ml actone, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.067 g white diastereomer solid salt was obtained by filtration with an output rate of

51%, in which the optical purity of R-salbutamol contained was 71.0% e.e.

Example 6

0.063 g (0.42mmol) L-(+)- tartrate and 0.2 g (0.84mmol) racemic salbutamol were dissolved in 10 ml ethanol (95%), the mixture was heated under reflux until it was clear, the mixture was cooled to room temperature, and then 0.125 g white diastereomer solid salt was obtained by filtration with an output rate of 95%, in which the optical purity of R-salbutamol contained was 58.4% e.e.

Example 7

0.063 g (0.42mmol) L-(+)- tartrate and 0.2 g (0.84mmol) racemic salbutamol were dissolved in 10 ml ethanol, the mixture was heated under reflux until it was clear, the mixture was cooled to room temperature, and then 0.224 g white diastereomer solid salt was obtained by filtration with an output rate of 171%, in which the optical purity of R-salbutamol contained was 10.6% e.e.

Example 8

0.063 g (0.42mmol) L-(+)- tartrate and 0.2 g (0.84mmol) racemic salbutamol were dissolved in 5 ml ethanol (95%), the mixture was heated under reflux until it was clear, the mixture was cooled to room temperature, and then 0.135 g white diastereomer solid salt was obtained by filtration with an output rate of 103%, in which the optical purity of R-salbutamol contained was 55.1% e.e.

Example 9

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 4 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 3 ml butanone, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.105 g white diastereomer solid salt was obtained by filtration with an output rate of 80%, in which the optical purity of R-salbutamol contained was 60.5% e.e.

Example 10

0.035 g (0.23mmol) L-(+)- tartrate was dissolved in 3 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 4 ml ethanol, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.079 g white diastereomer solid salt was obtained by filtration with an output rate of 77%, in which the optical purity of R-salbutamol contained was 63.6% e.e.

Example 11

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 3 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 4 ml cyclohexanone, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.071 g white diastereomer solid salt was obtained by filtration with an output rate of 54%, in which the optical purity of R-salbutamol contained was 77.3% e.e.

Example 12

0.063 g (0.42mmol) L-(+)- tartrate was dissolved in 3 ml methanol and 0.2 g (0.84mmol) racemic salbutamol was dissolved in 3 ml normal butyl alcohol, both of them were mixed, the mixture was heated under reflux for 10 minutes, the mixture was cooled to room temperature, and then 0.111 g white diastereomer solid salt was obtained by filtration with an output rate of 84%, in which the optical purity of R-salbutamol contained was 63.2% e.e.

Example 13

0.32 g (2.13mmol) L-(+)- tartrate and 1.00 g (4.18mmol) racemic salbutamol were dissolved in 25 ml ethanol (95%), the mixture was heated under reflux until it was clear, the mixture was cooled to room temperature, 0.683 g white diastereomer solid salt was obtained by filtration with an output rate of 104%, in which the optical purity of R-salbutamol contained was 56.5% e.e. Then 0.414 g white diastereomer solid salt was obtained by recrystallizing 0.660 g product (56.5% e.e) obtained by the above step with 1 ml water and 21 ml ethanol, and the output rate of recrystallizing was 63%, in which the optical purity of R-salbutamol contained was 85.8% e.e. After that, 0.348 g white diastereomer solid salt was obtained by recrystallizing 0.398 g product (85.8% e.e)

obtained by a first recrystallization with 0.6 ml water and 17 ml ethanol, and the output rate of recrystallizing was 88%, in which the optical purity of R-salbutamol contained was 94.2% e.e. Then, 0.332 g white diastereomer solid salt was obtained by recrystallizing 0.332 g product (94.2% e.e) obtained by a second recrystallization with 0.5 ml water and 10 ml ethanol, and the output rate of recrystallizing was 85%, in which the optical purity of R-salbutamol contained was 96.7% e.e.

Example 14

1.30 g (2.13mmol) L-(+)- tartrate and 4 .00 g (4.18mmol) racemic salbutamol were dissolved in 100 ml ethanol(95%), the mixture was heated under reflux until it was clear, the mixture was cooled to room temperature, 3.738 g white diastereomer solid salt was obtained by filtration with an output rate of 141%, in which the optical purity of R-salbutamol contained was 19.5% e.e. Then, 97.6% e.e white diastereomer solid salt was obtained by recrystallizing the product of the above step four times, and the output rate of recrystallizing was 38%. (a) 0.185 g white diastereomer solid salt was obtained by recrystallizing 97.6% e.e diastereomer solid salt with 3 ml methanol and 0.2 ml water and 4 ml ethanol, and the output rate of recrystallizing was 84%, in which the optical purity of R-salbutamol contained was 99.2% e.e. (b) 0.185 g white diastereomer solid salt was obtained by recrystallizing 97.6% e.e diastereomer solid salt with 0.5 ml water and 0.3 ml methanol and 5 ml acetone, and the output rate of recrystallizing was 84%, in which the optical purity of R-salbutamol contained was 99.3% e.e, $[\alpha]_D^{20}$=-24.3°(c=0.25, water), there was the main peak as follows in an X-ray power diffraction pattern:

| The value of $d_{-1}$/ angstrom | Comparative intensity |
|---|---|
| 16.05 | w |
| 8.11 | vs |
| 7.89 | s |
| 7.25 | m |
| 6.46 | m |
| 5.30 | m |

| | |
|---|---|
| 5.01 | m |
| 4.87 | m |
| 4.44 | s |
| 3.93 | vs |
| 3.80 | m |
| 3.62 | m |
| 3.42 | m |
| 3.24 | m |
| 3.10 | w |
| 2.86 | w |
| 2.71 | w |
| 2.49 | w |
| 2.32 | w |
| 2.13 | w |